

Response of the Hodgkin-Huxley neuron to a periodic sequence of biphasic pulses

L. S. Borkowski

Department of Physics, Adam Mickiewicz University, Umultowska 85, 61-614
Poznan, Poland

Abstract. We study the response of the Hodgkin-Huxley neuron stimulated periodically by biphasic rectangular current pulses. The optimal response for charge-balanced input is obtained for cathodic-first pulses with an inter-phase gap (IPG) approximately equal 5ms. For short pulses the topology of the global bifurcation diagram in the period-amplitude plane is approximately invariant with respect to the pulse polarity and shape details. If stimuli are delivered at neuron's resonant frequencies the firing rate is a continuous function of pulse amplitude. At nonresonant frequencies the quiescent state and the firing state coexist over a range of amplitude values and the transition to excitability is a discontinuous one. There is a multimodal odd-all transition between the 2:1 and 3:1 locked-in states. A strong antiresonant effect is found between the states 3:1 and 4:1, where the modes $(2 + 3n) : 1$, $n = 0, 1, 2, \dots$, are entirely absent. At high frequencies the excitation threshold is a nonmonotonic function of the stimulus and the perithreshold region is bistable, with the quiescent state coexisting with either a regular or chaotic firing.

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1. Introduction

Stimulation of neural fibers with a train of electric current pulses has become standard procedure in several areas of clinical practice. This encompasses, but is not limited to, cochlear and retinal prostheses[1, 2], deep brain stimulation[3], as well as high-frequency conduction block of peripheral nerves[4]. Typically such devices should minimize charge and energy per pulse. The minimum current amplitude required for the neuron to spike and its dependence on stimulation frequency and pulse shape are among the basic properties measured in experiment. The injected charge should be kept at safe levels, mainly to avoid changes in the chemical content in the tissue near the electrode which could damage the tissue or cause the electrode corrosion[5]. Typically the minimum charge injected by the electrode needed by the neuron to spike occurs at a vanishing pulse width whereas the optimization of the energy of the pulse occurs at a certain nonzero width[6, 7, 8]. If pulses are short various, different waveforms have very similar efficiency[9]. Differences become apparent for longer pulses. Most cochlear implants use charge-balanced biphasic (BP) stimulation. Studies of auditory nerve fibers (ANF) can be reduced[10, 11] by introducing a delay between standard BP pulses commonly used in cochlear implants.

Irregular firing and desynchronization among a group of ANF is usually attributed to irregular synaptic input and physiological noise[12, 13]. It must be kept in mind however that neurons themselves are strongly nonlinear systems and are capable of irregular firing even in the absence of noise[14, 15]. O’Gorman et al. showed recently[16, 17] that a dynamic instability is a plausible explanation of firing irregularities in stimulated ANF. Using the FitzHugh-Nagumo (FHN) model[18], they obtained a positive Lyapunov exponent which is consistent with experiments, where mutual desynchronization between similarly stimulated fibers was observed. Electrically stimulated ANF fire regularly at low rates and irregularly at high rates of stimulation. The sensitivity in this regime bears some resemblance to experimental results on electrically stimulated ANF[19, 20]. The FHN model is a simplification of the more complex Hodgkin-Huxley (HH) equations. The HH model subject to a high frequency monophasic pulse current also exhibits a strongly nonlinear response[14], including nonmonotonic dependence of the firing rate on pulse amplitude and a high coefficient of variation of interspike intervals. There is a significant slowing down of average response frequencies in the vicinity of the multimodal transition where the parity of response modes is changed. Therefore it would be useful to know if the HH model behaves similarly also for charge-balanced inputs.

The present work may also help in solving problems related to the spike timing control in resonant neurons. The ability to control precisely the time at which neuron will emit a spike if a firing event occurred at some earlier time[8] is important in some applications. In general the minimum time to fire is a complex issue, dependent on imposed constraints, initial conditions and details of the model. One of the main complications is the bistability of the HH model. The obtained minimum firing time and the minimum impulse strength may fall within a bistable regime, where a small change of the neuron’s initial state may lead to no spike. Knowing the location of bistable regimes in the response diagram of a typical resonant neuron should help in designing spike control algorithms. Here the HH model serves as a convenient testing ground.

2. Model and results

We will try to provide some support to earlier experimental findings using the basic HH model. While this model has no direct application in the clinical setting we can improve our understanding of clinical experiments by studying the excitation threshold's dependence on stimulus waveform in simplified models.

We will analyze the response of the HH neuron to periodic biphasic charge balanced pulses. Such stimuli were investigated experimentally[21, 11, 22] and theoretically by several groups[10, 11, 23, 24]. The requirement of charge neutrality is imposed to avoid tissue damage.

We consider the model with the classic parameter set and rate constants[25],

$$C \frac{dV}{dt} = -I_{Na} - I_K - I_L + I_{app}, \quad (1)$$

where I_{Na} , I_K , I_L , I_{app} , are the sodium, potassium, leak, and external current, respectively. $C = 1\mu\text{F}/\text{cm}^2$ is the membrane capacitance. The input current is a periodic set of rectangular steps of height I_0 and width τ . The simulations are carried out with the time step of 0.001ms and are run for 40s, discarding the initial 4s. Fig. 1 shows the form of biphasic pulses used in the calculation. The emphasis of this work is on the charge-balanced stimulus shown in the top part of Fig. 1. However the dependence of the threshold on IPG at different stimulation frequencies will also be presented for the monopolar biphasic pulses, shown in the bottom diagram of Fig. 1. Stimuli of this form are often used in cochlear[10, 11, 23, 24] and visual[1, 2] neural prostheses, as well as deep brain and muscle stimulation[5]. Electrical stimulation protocols have been used to learn about cortical function[26] and vestibulo-ocular reflex eye movements in chinchillas[27]. High-frequency biphasic current pulses may also be useful in reversible peripheral nerve block that would be desirable in some clinical applications[4]. We will investigate the influence of the amplitude of the pulses as well as their period T_i , width τ and delay τ_1 between the onsets of the two phases.

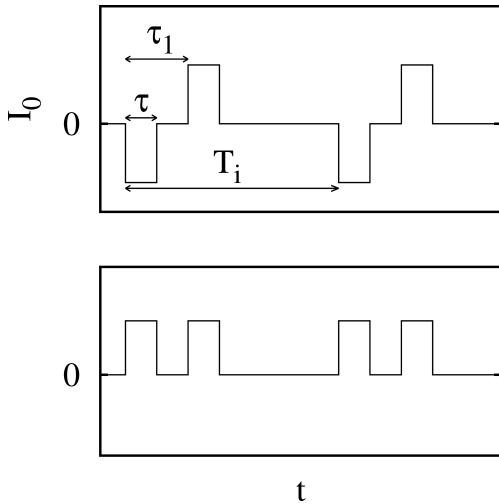


Figure 1. Stimulus waveform used in the calculations: charge-balanced biphasic form with delay (upper) and monophasic pulses with delay (lower). The delay between the cathodic and anodic phase is τ_1 and τ is the width of each phase.

Fig. 2 shows the global bifurcation diagram for a charge-balanced biphasic current with no delay between the cathodic and anodic part, i.e. $\tau = \tau_1$. The firing rate f_o/f_i , where f_o is the firing frequency in response to the stimulus frequency f_i , is a continuous function of the current amplitude near the resonance, $T_i \sim T_{res} \simeq 17\text{ms}$. T_i is the period of the stimulus. The response at antiresonant frequencies is bistable. Boundaries of bistable areas are found using a continuation algorithm, in which end values from the previous iteration are used as initial conditions for a new parameter set.

The overall topology of this diagram closely resembles the result for monophasic monopolar pulses[28]. In the high frequency limit the threshold is a complicated function of T_i with a maximum near $T_i = 5.5\text{ms}$, which is approximately 1/3 of the resonance period T_{res} . Nonmonotonic behavior of hearing threshold was also observed in experiments in cochlear implant users[29]. Below $T_i = 8\text{ms}$ the entire perithreshold region is bistable. Here the quiescent state coexists with either a locked-in or a chaotically firing state. Which of these solutions is obtained depends sensitively on initial conditions.

The firing frequency depends nonmonotonically on T_i . Fig. 3 shows f_o vs. T_i for I_0 slightly above threshold. The largest deviation from the resonant frequency occurs between the 2:1 and 3:1 states, near $T_i = 7.5\text{ms}$. This is a signature of a dynamic instability associated with the competition of even and odd modes[14].

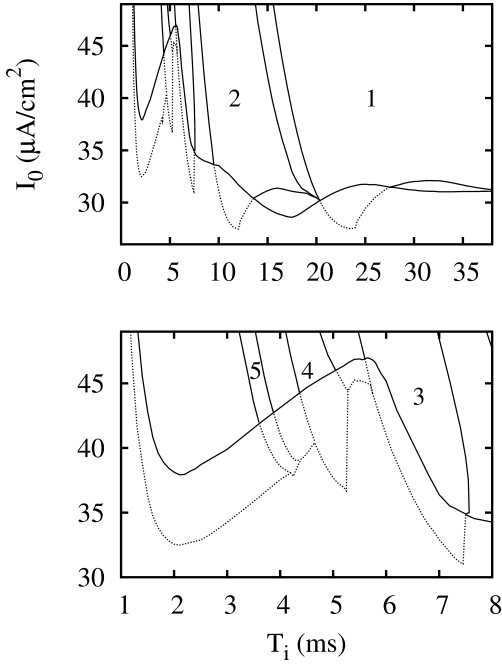


Figure 2. Response diagram for a biphasic stimulus with no delay between the anodic and the cathodic part of a pulse (upper). The lower portion shows the high frequency limit in more detail. Borders of bistable regions are marked with a dotted line. The resonance near $T_i = 17\text{ms}$ is dominated by the 3:1 state and higher order states. The second resonance near $T_i = 34\text{ms}$ is occupied by modes higher than 1:1 (see also Ref. [28]).

In an earlier article we have shown that the HH neuron responding to periodic

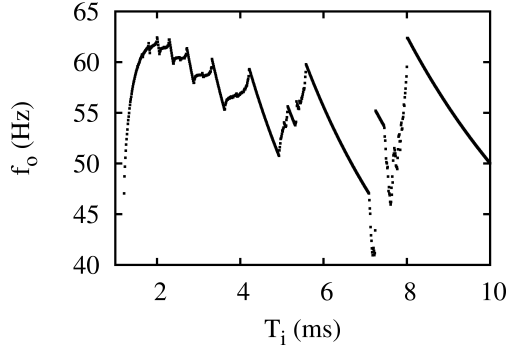


Figure 3. The firing frequency in the limit of high stimulation frequency for a biphasic pulse at $I_0 = 47\mu\text{A}/\text{cm}^2$. The response between the mode-locked intervals is nonmonotonic and highly irregular.

sequence of monophasic pulses undergoes a multimodal odd-all[14] and even-all transition[28] in some regions of parameter space. Fig. 4 shows the minimum of the firing rate occurring between the 2:1 and 3:1 locked states for pulse amplitude $I_0 = 35\mu\text{A}/\text{cm}^2$. In the lower part of Fig. 4 we can clearly see that the weight of even modes is nonzero only for T_i above the minimum of the firing rate. For smaller T_i only odd modes exist. The role of the mode parity is easier to understand if we remember that $2T_i$, where $T_i \simeq 8.5\text{ms}$ is approximately the resonant period. The competition of the odd and even modes in Fig. 4 accompanies the transition between the resonant and antiresonant regime. The vanishing of even modes below $T_i \simeq 8.4\text{ms}$ and a significant decrease of the firing rate are a clear signature of the antiresonant regime. Odd multiples of $T_i = 8.4\text{ms}$ are associated with antiresonant stimulation frequencies.

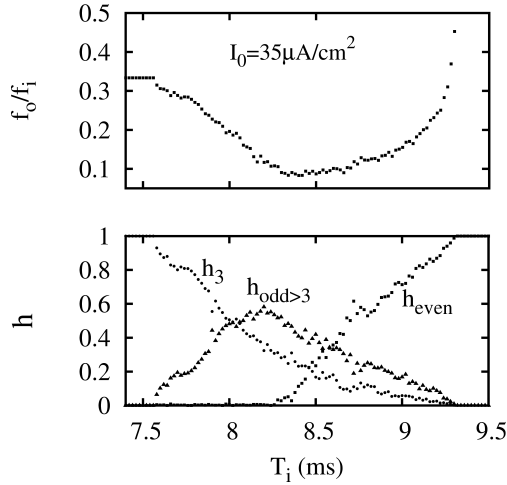


Figure 4. The firing rate (upper) and the histogram weight of odd and even modes (lower) in the vicinity of the odd-all multimodal transition for a biphasic pulse at $I_0 = 35\mu\text{A}/\text{cm}^2$. Even modes appear only above the minimum of f_o/f_i . An interspike interval is classified as belonging to the n^{th} mode if it falls between $(n - 1/2)T_i$ and $(n + 1/2)T_i$.

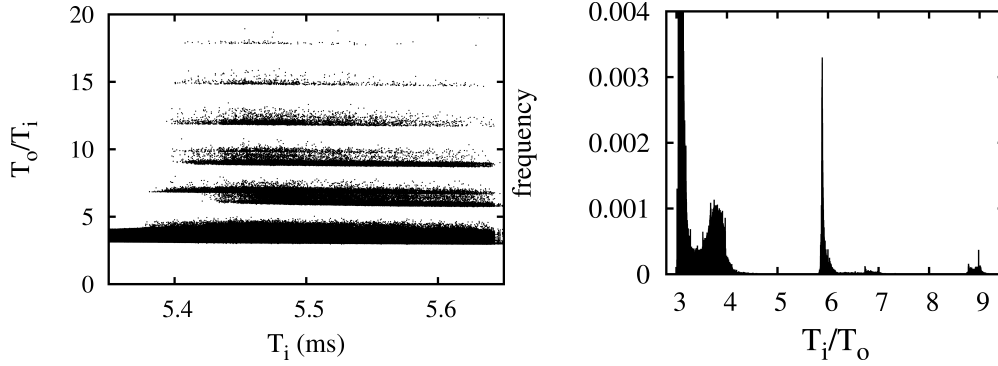


Figure 5. Upper: The ratio of the output period T_o to the input period T_i between the 3:1 and 4:1 entrained states for a biphasic pulse at $I_0 = 45.8 \mu\text{A}/\text{cm}^2$. Lower: Histogram of response modes at $T_i = 5.55\text{ms}$ and $I_0 = 45.8 \mu\text{A}/\text{cm}^2$. The histogram bin size is 0.01ms. Note the absence of modes 5,8,11,14, and 17.

Another interesting effect occurs between the 3:1 and 4:1 locked states at high frequencies. Bands of T_o vs. T_i values are shown in Fig. 5. Note the absence of all modes $(5+n):1$, where n is a nonnegative integer. This is a consequence of the fact that the product $(5+n)T_i$ falls in an antiresonant regime for $T_i \simeq 5.5\text{ms}$. Since this is a qualitative effect it may provide a strong test of applicability of the Hodgkin-Huxley model in various contexts. Qualitatively similar result should be obtained for other types of pulses as well.

Fig. 6 shows the excitation threshold as a function of the delay between the anodic and the cathodic phases of the pulse, for four choices of the stimulus period. In each case the optimum τ_1 is about 5ms. If the input period is in the antiresonance regime, i.e. for $T_i = 11$ and 23ms, there are two thresholds because of bistability, both of which have minima at similar values of τ_1 . The upper threshold where the transition to excitability occurs through a Hopf bifurcation, has a maximum at approximately $\tau_1 = 13\text{ms}$. This antiresonant feature occurs at the same τ_1 also for $T_i = 34\text{ms}$. Lower thresholds for biphasic cathodic-first stimuli were also observed in Refs. [30, 31, 32] and calculated by Smit et al.[24] in an ANF model containing persistent sodium and slow potassium currents. The shape of the curve in Fig. 6 for $T_i = 34\text{ms}$ is reminiscent of a phase response curve for the Hodgkin-Huxley model[8].

The minimum threshold is obtained when the stimulus is tuned to the natural resonance of the neuron. The maximum delay for the interaction between the cathodic and anodic phase to occur is approximately 18ms. The cathodic phase of the magnitude shown in the bottom diagram of Fig. 6 induces subthreshold oscillations with a resonant period. The spike-triggered average of stimulus $I(t)$ for isolated spikes in the HH model driven by Gaussian random noise current with a short correlation time also indicates the preference of the neuron for approximately 5ms separation between the negative and positive parts of the current[33]. This is a reflection of the HH neuron's internal dynamics in which the sodium channel remain open for about 5ms from the stimulus onset. The bifurcation diagram with optimal IPG, $\tau_1 \simeq 5\text{ms}$, closely resembles Fig. 2. The only significant difference is a shift to lower values of I_0 .

The threshold for biphasic monopolar pulses is shown in Fig. 8. For $T_i \leq T_{res}$ the most regular input signal with equally spaced pulses is also the least likely to elicit spiking. The meaning of parameters is as in Fig. 1. When the regularity of the signal is distorted the threshold decreases.

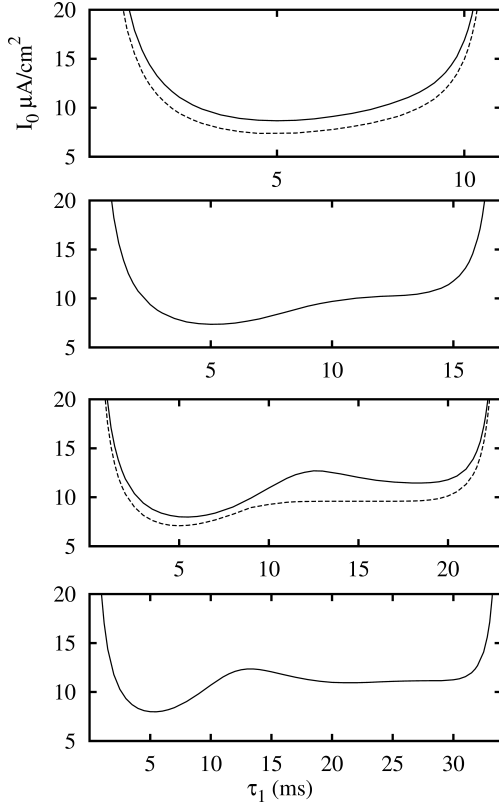


Figure 6. Excitation edge for different interpulse separation as a function of time difference between the cathodic and anodic phase. From top to bottom: $T_i = 11, 17, 23$, and 34 ms, for stimulation by rectangular current pulses of width $\tau = 0.6$ ms and height I_0 . For different pulse frequencies the minimum occurs at $\tau_1 \simeq 5$ ms separation between the cathodic and the anodic phase. The threshold is bistable for $T_i = 11$ ms and 23 ms.

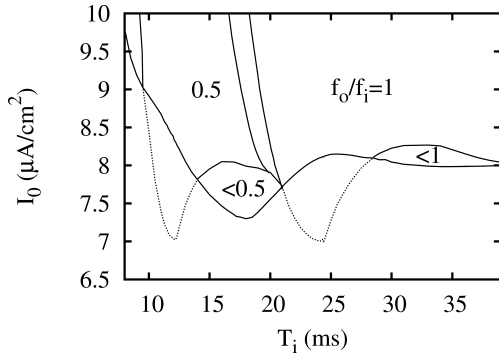


Figure 7. Response diagram for stimulus with an optimal inter-phase gap. Bistable regions are marked *b*. The resonance area near $T_i = 17$ ms is dominated by the 3:1 state and higher order states. The second resonance near $T_i = 34$ ms is occupied by modes higher than 1:1.

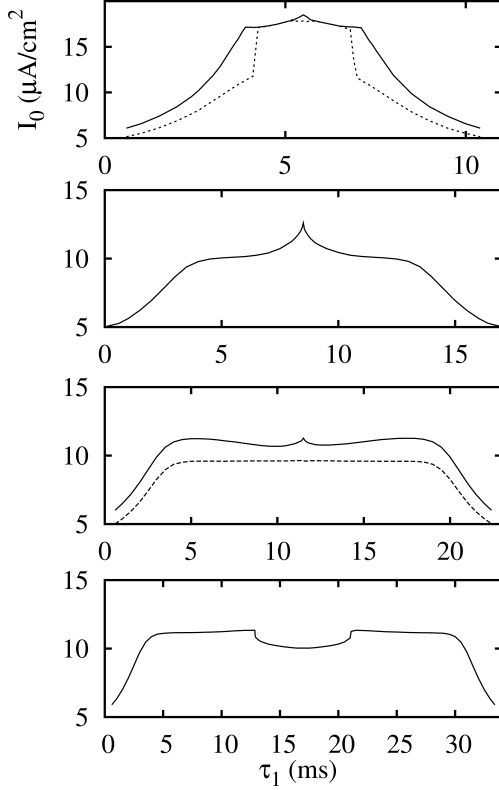


Figure 8. Excitation edge for a double pulse as a function separation between the leading and the trailing phase. The diagrams from top to bottom are drawn for $T_i = 11, 17, 23$, and 34 ms, respectively.

Comparing Fig. 7 to Fig. 2, we can conclude that the topology of the response diagram does not depend on the size of IPG for $\tau_1 < 5$ ms. The same is likely to be true for all types of periodic short pulses irrespective of details of their time dependence. This is an illustration of the well known fact that the HH neuron has a charge threshold property. When a relatively strong current is delivered in a short time, the voltage change is mainly determined by the capacitive current[34, 35, 36].

In neural electrical stimulation the main safety factors are the amount of charge transferred in a single pulse, Q_{th} , and energy per spike, E_{th} , needed to evoke spiking,

$$Q_{th} \sim \int_0^\tau I_{th}(t)dt \quad (2)$$

$$E_{th} \sim \int_0^\tau I_{th}^2(t)dt, \quad (3)$$

where I_{th} is the threshold current amplitude. Fig. 9 shows the threshold charge at $T_i = 17$ ms as a function of the phase width τ for $\tau_1 = 5$ ms. The charge-duration curve in Fig. 9 implies the use of short pulses in stimulation protocols if the injected charge is to be minimized. In practice, pulses lasting tens of microseconds approach the minimum charge condition sufficiently well and are often a reasonable solution in the design of neural prostheses. During this relatively short time one may be able

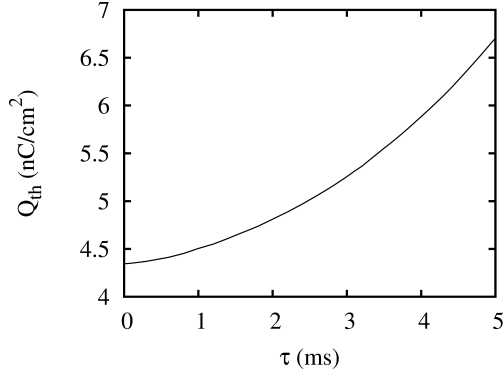


Figure 9. Threshold charge as a function of the τ for $T_i = 17\text{ms}$ and $\tau_1 = 5\text{ms}$. The minimum occurs at $\tau = 0$ which means that the most effective pulses are those with vanishing width.

to avoid Faradaic reactions that would occur at higher levels of total charge with longer pulses. Similar conclusion was reached in a study of Sahin and Tie[7] who investigated effects of non-rectangular waveforms on threshold both experimentally and theoretically within a simple local model of a mammalian nerve[37, 38]. Their model is similar to the HH model except for the absence of the potassium channel. However if the main limiting factor is the energy delivered per pulse, then finite τ is preferable, see Fig. 10. Qualitatively similar result was obtained for different waveforms in Ref. [7].

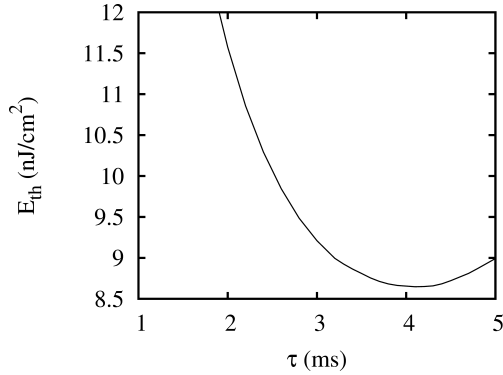


Figure 10. Threshold energy at the resonance frequency, $T_i = 17\text{ms}$, and $\tau_1 = 5\text{ms}$, as a function of the time separation between the leading edge of the cathodic phase and the leading edge of the anodic phase. The minimum occurs near $\tau = 4\text{ms}$.

3. Conclusions

Studies of threshold behavior of resonant neurons may help designing future cochlear implants. Nonlinear instability present in the HH model may provide important clues to understanding ANF response to high-frequency stimulation. O’Gorman et al. used the FHN model to explain irregular firing of auditory nerve fibers and the lack of

synchronization of response to external drive[16]. This instability may be related to the recently discovered parity transitions of response modes[14, 28]. It is important to realize that a resonant cell such as the HH neuron fires regularly in resonant regimes and irregularly in antiresonant regimes. In our work on the HH model stimulated by monopolar monophasic pulses we found the odd-all multimodal transition[14, 15], in which the vanishing of even response modes is accompanied by a local minimum of the firing rate. This effect occurs between the 2:1 and 3:1 states and is most pronounced near excitation threshold. Here we found the same phenomenon in the HH neuron driven by charge-balanced biphasic current pulses. We also discovered a new effect: the vanishing of the modes 2, 5, 8, ... in the regime of irregular firing between 3:1 and 4:1 states. These antiresonant effects are quite general and do not depend on details of pulse shape or polarity of the current pulse.

The firing threshold of the HH model is a nonmonotonic function of frequency with the minimum at the main resonance frequency. A local minimum exists also at very high stimulation rate. At the resonant frequencies the solution is always unique and the firing rate is a continuous function of the pulse amplitude. At non-resonant frequencies the HH neuron is bistable, i.e. the firing state coexists with the excitable state, and the transition to excitability is discontinuous. Charge-balancing has no effect on the topology of the global bifurcation diagram in the period-amplitude plane. Fig. 2 closely resembles results obtained for monophasic stimulation[28]. These properties are quite general, provided the width of the current pulses is sufficiently small, which implies $\tau_1 < 5\text{ms}$ for the classic HH parameter set, and should hold for other, non-rectangular pulse shapes.

Results in Figs. 6 and 10 indicate that IPG giving the lowest excitability threshold of the HH membrane is approximately 4 – 5ms. The minimum threshold approaches that of the excitatory monophasic current pulse and is obtained for $\tau_1 \simeq 5\text{ms}$. The decrease of threshold associated with the increase of IPG is consistent with experimental measurements[10]. Similar result was obtained for biphasic pulses with long IPG in a phenomenological model of the electrically stimulated human ANF[23]. Our results are also consistent with the work of Carlyon et al.[11] who studied human behavioral thresholds for trains of biphasic pulses applied to a single channel of cochlear implants as a function of IPG. The threshold decreased for IPGs up to several milliseconds when the phases of the pulse were of opposite polarity. The IPG of about 4ms also approximately minimizes the energy delivered per pulse. The optimal stimulation approach may include a Gaussian noise superposed on the input signal[39]. Small amounts of noise were shown to improve detection of faint signals, improve temporal resolution and regularize strongly irregular firing in regimes of dynamic instabilities.

References

- [1] Schmidt E M, Bak M J, Hambrecht F T, Kufta C V, O'Rourke D K and Vallabhanath P 1996 *Brain* **119** 507
- [2] Humayun M S, de Juan Jr. E, Weiland J D, Dagnelie G, Katona S, Greenberg R and Suzuki S 1999 *Vision Res* **39** 2569
- [3] McIntyre C C and Grill W M 2000 *Ann. Biomed. Eng.* **28** 219
- [4] Tai C, de Groat W C and Roppolo J R 2005 *IEEE Trans. Biomed. Eng.* **52** 1323
- [5] Merrill D R, Bikson M and Jefferys J G R 2005 *J. Neurosci. Meth.* **141** 171
- [6] Wessale J L, Geddes L A, Ayers G M and Foster K S 1992 *Ann. Biomed. Eng.* **20** 237
- [7] Sahin M and Tie Y 2007 *J. Neural Eng.* **4** 227
- [8] Danzl P, Nabi A and Moehlis J 2010 *Discrete Contin. Dynam. Systems* **28**, 1413

- [9] Wongsarnpigoon A, Woock J P and Grill W M 2010 *IEEE Trans. Neural Syst. Rehabil. Eng.* **18** 319
- [10] Shepherd R K and Javel E 1999 *Hearing Res.* **130** 171
- [11] Carlyon R P, van Wieringen A, Deeks J M, Long C J, Lyzenga J and Wouters J 2005 *Hearing Res.* **210**
- [12] Morse R P and Evans E F 1996 *Nature Medicine* **2** 860
- [13] Moss F, Chiou-Tan F and Klinke R 1996 *Nature Medicine* **2** 860
- [14] Borkowski L S 2009 *Phys. Rev. E* **80** 051914
- [15] Borkowski L S 2010 *Phys. Rev. E* **82** 041909
- [16] O’Gorman D E, White J A and Shera C A 2009 *J. Assoc. Res. Otolaryngol.* **10** 251
- [17] O’Gorman D E, Colburn H S and Shera C A 2010 *J. Acoust. Soc. Am.* **128** EL300
- [18] FitzHugh R 1961 *Biophys. J.* **1** 445
- [19] van den Honert C and Stypulkowski P H 1987 *Hearing Res.* **29** 207
- [20] Javel E and Viemeister N F 2000 *J. Acoust. Soc. Am.* **107** 908
- [21] McKay C M and Henshall K R 2003 *Hearing Res.* **215** 47
- [22] Prado-Gutierrez P, Fewster L M, Heasman J M, McKay C M and Shepherd R K 2006 *Hearing Res.* **215** 47
- [23] Macherey O, Carlyon R P, van Wieringen A and Wouters J 2007 *J. Assoc. Res. Otolaryngol.* **8** 84
- [24] Smit J E, Hanekom T, van Wieringen A, Wouters J and Hanekom J J 2010 *Hearing Res.* **269** 12
- [25] Hodgkin A L and Huxley A F 1952 *J. Physiol. (London)* **117** 500
- [26] Tehovnik E J, Tolia S A, Sultan F, Slocum W M and Logothetis N K 2006 *J. Neurophysiol.* **96** 512
- [27] Davidovics N S, Fridman G Y, Chiang B and Santina C C D 2011 *IEEE Trans. Neural Syst. Rehabil. Eng.* **19** 84
- [28] Borkowski L S 2011 *Phys. Rev. E, to appear*
- [29] van Wieringen A, Carlyon R P, Macherey O and Wouters J 2006 *Hearing Res.* **220** 49
- [30] van Wieringen A, Carlyon R P, Laneau J and Wouters J 2005 *Hearing Res.* **200** 73
- [31] van Wieringen A, Macherey O, Carlyon R P, Deeks J M and Wouters J 2008 *Hearing Res.* **242** 154
- [32] Macherey O, van Wieringen A, Carlyon R P, Deeks J M and Wouters J 2006 *J. Assoc. Res. Otolaryngol.* **7** 253
- [33] Agüera y Arcas B, Fairhall A L and Bialek W 2003 *Neural Comput.* **15** 1715
- [34] Hodgkin A L and Rushton W A H 1946 *Proc. Roy. Soc. Lond. B* **133** 444
- [35] Noble D and Stein R B 1966 *J. Physiol.* **187** 129
- [36] Koch C 1999 *Biophysics of computation* (Oxford University Press) p 392
- [37] Chiu S Y, Ritchie J M, Rogart R B and Stagg D 1979 *J. Physiol.* **292** 149
- [38] Sweeney J D, Mortimer J T and Durand D 1987 *IEEE 9th Ann. Conf. Eng. Med. Biol. Soc. (Boston, MA)*
- [39] Matsuoka A J, Abbas P J, Rubinstein J T and Miller C A 2000 *Hearing Res.* **149** 129